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EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,105	LAEREMANS ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 46-94* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,46-54,61,63-67,70,71,74,75,78,79,82,87,90,91 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 55-60, 62, 68-69, 72-73, 76-77, 80-81, 83-86, 88-89, and 92-93.

DETAILED ACTION

1. Claims 1 and 46-94 are pending.

2. Claims 55-60, 62, 68-69, 72-73, 76-77, 80-81, 83-86, 88-89, and 92-93 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1, 46-54, 61, 63-67, 70-71, 74-75, 78-79, 82, 87, 90-91, and 94, drawn to an anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one single domain antibody directed against EGFR, an anti-EGFR polypeptide of SEQ ID NO: 6, a kit comprising said single domain antibody direct against EGFR, and a therapeutic composition comprising said single domain antibody direct against EGFR, are being acted upon in this Office Action.

4. The Brief Description of Figures **2** and **5** is objected to because the labeling of the Figure "Figure **2-1**", "Figure **2-2**", "Figure **5-1**" and "Figure **5-2**" is inconsistent with the Brief Description of Figures **2** and **5**. Correction is required.

5. The following new grounds of rejections are necessitated by the amendment filed July 10, 2008.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 46-54, 61, 63-67, 70-71, 74-75, 78-79, 82, 87, 90-91, and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated single domain antibody directed against Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody sequence represented by SEQ ID NO: 6, (2) the said single domain antibody binds to EGFR with an affinity of at least 1×10^{-6} M, (3) a humanized Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 13, (4) a composition comprising the isolated anti-Epidermal Growth

Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 6 and a carrier, (5) a kit comprising the isolated anti-Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 6 for detecting EGFR polypeptide and bispecific single domain antibody that binds specifically to EGFR and serum albumin comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 27-40 for detection assays, **does not** reasonably provide enablement for (1) any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6, (2) a functional portion of SEQ ID NO: 6 wherein the functional portion is capable of binding its target with an affinity of at least 1 x 10^{-6} M; (3) any functional portion of SEQ ID NO: 6 wherein the functional portion comprises any partial deletion of the complete amino acid sequence and still maintains the binding site(s) and protein domain(s) necessary for the binding of and interaction with EGFR as set forth in claim 46, (4) any single domain antibody mentioned above wherein the one or more of the Camelidae amino acids of said single domain antibody are replaced by counterpart amino acids of any human consensus sequence, (5) any single domain antibody directed against any EGFR mentioned above comprising any one or more mutations in the framework region (FR): FR1 positions 1, 5, 28 and 30; the hallmark amino acid at position 44 and 45 in FR2; FR3 residues 74, 75, 76, 83, 84, 93 and 94; and positions 103, 104, 108 and 111 in FR4; wherein the numbering is according to the Kabat numbering as set forth in claims 46-54, (6) any anti-EGFR polypeptide consisting essentially of two or more single domain antibodies directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is (a) any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6, (b) a functional portion of SEQ ID NO: 6 wherein the functional portion is capable of binding its target with an affinity of at least 1 x 10^{-6} M; (c) any functional portion of SEQ ID NO: 6 wherein the functional portion comprises any partial deletion of the complete amino acid sequence and still maintains the binding site(s) and protein domain(s) necessary for the binding of and interaction with EGFR or (d) any two or more single domains antibodies are identical in sequence fused genetically, or linked to each other directly, or trivalent or tetravalent molecule, (7) any composition comprising any single domain antibody mentioned above as set forth in claims 67, 70-71, 74-75, (8) any pharmaceutical composition comprising any single domain antibody mentioned above and a carrier as set forth in claims 79, 81-82, and (9) any kit comprising any single domain antibody mentioned above as set forth in claim 87, 90-91 and 94. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Enablement is not commensurate in scope with how to make and use any single domain antibody directed against any EGFR mentioned above other than the sequence represented by SEQ ID NO: 6.

The specification at page 20 defines "a homologous sequence" as a homologous sequence of the present invention may comprise any additions, any deletions or any substitutions of any one or more amino acids, which do not substantially alter the functional characteristics of the polypeptides of the invention. For the anti-Epidermal Growth Factor Receptor polypeptides, the number of amino acid deletions or substitutions is preferably up to 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70 amino acids". "A homologous sequence according to the present invention may be a sequence modified by the addition, deletion or substitution of amino acids, said modification not substantially altering the functional characteristics compared with the unmodified polypeptide". "A homologous sequence according to the present invention may be a sequence which exists in other *Camelidae* species such as, for example, camel, dromedary, llama, vicuna, alpaca and guanaco".

The specification discloses only isolated single domain antibody VHH from *Camelidae* that binds specifically to Epidermal Growth Factor Receptor (EGFR) such as the ones shown in Table 4 wherein the antibody comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1-22. The specification discloses these single domain antibodies selected for binding to EGFR and for the ability to internalize through cell surface EGFR, see page 50. The specification discloses humanized VHH represented by SEQ ID NO: 13, see page 15, lines 9-21. The specification further discloses the isolated single domain antibody VHH from

Camelidae that binds to EGFR further comprising a single domain antibody VHH that binds to serum albumin corresponds to a sequence selected from the group consisting of SEQ ID NO: 27-40 as shown in Table 5. There is no disclosure whether any such anti-EGFR can treat, much less *prevent* any disorders relating to any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

At the time of filing, the specification does not teach how to make and use any single domain antibody that binds to any EGFR directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6 other than the specific single domain antibody that binds to EGFR represented by SEQ ID NO: 6. There is no guidance as to which amino acids within the sequence represented by SEQ ID NO: 6 to be substituted, deleted and/or added such that the single domain antibody still maintain its binding specificity to EGFR. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same binding specificity are limited in any antibody and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the SEQ ID NO: 6 and maintains the same biological activity.

At the time of the invention, there was a high level of unpredictability associated with altering a protein sequence with an expectation that the protein will maintain the same desired biological activity. For example, it is well established in the art that the even minor changes in the amino acid sequences of the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc Natl Acad Sci USA 1982 Vol 79 page 1979-1983; PTO 892). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Schlaeppi et al (of record, J Cancer Res Clin Oncol 125: 336-342, 1999; PTO 892) teach substitutions even just three residues (Q87R, G88K, Q89K) located on the major surface loop β5 to β6 of VEGF, resulted in complete loss of binding (see abstract, in particular). Schlaeppi et al

further teach that antibody that binds to the dimeric form of VEGF is conformational dependent (see abstract, in particular).

Winkler et al (of record, J Immunology 165: 4505-4514, 2000; PTO 892) teach a single amino acid changes in the variable region of any antibody may substantially change the binding specificity of antibody (see abstract, in particular).

Zhu et al (of record, Investigational New Drugs 17: 195-212, 1999; PTO 892) teach despite high sequence homology (i.e. 85%) between mouse FLK-1 and its human homolog, KDR, none of the blocking anti-KDR antibodies produced cross-reacts with Flk-1. Consequently, tumors grown in mice, which recruit the mouse vasculature, are not appropriate models to evaluate the anti-angiogenesis therapy *in vivo* (see page 201, col. 2, last paragraph, in particular).

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the length of the antibody heavy chain CDR3 is critical for antigen specific binding site (see abstract, in particular).

Given the lack of guidance as to structure associated with binding specificity of such single domain antibody directed to any EGFR, the lack of direction or in vivo working examples, the breadth of the claims, which encompass innumerable possible modification that encompassed substitution, deletion, addition and/or combination thereof and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

Further, the specification discloses single domain antibodies were raised in llamas. The specification defines VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, dromedary, llama, vicuña, alpaca and guanaco. However, no other VHH molecules that bind to EGFR and/or serum albumin are produced in other species such as camel, dromedary, vicuña, alpaca and guanaco. Other than the single domain antibodies represented by SEQ ID NO: 1-22, the specification does not teach any single domain antibody that binds to EGFR from other species.

With respect to homologous sequence, functional fragment and functional portion of a homologous sequence of the full length single domain antibody or anti-EGFR polypeptide (claims 8-9), the claim encompasses a genus of single domain antibody directed against EGFR for the claimed anti-EGFR polypeptide, any functional portion or any functional portion of any homologous sequence. The specification discloses only single domain antibodies directed against EGFR from llamas. One species is not a representative of the genus Camelidae.

With respect to "functional portion", the specification at page 21 defines a "functional portion" as it refers to the polypeptide sequence an anti-Epidermal Growth Factor Receptor polypeptide refers to less than 100% of the sequence *(e.g.,* 99%, 90%, 80%, 70%, 60% 50% etc.), but comprising 5 or more amino acids or 15 or more nucleotides. There is no showing of any functional portion of SEQ ID NO: 6 having at least 50% difference to SEQ ID NO: 6 still binds and interacts with which EGFR.

With respect to "functional portion wherein the portion comprises any partial deletion of SEQ ID NO: 6", SEQ ID NO: 6 is the smallest antibody fragment (single domain antibody VHH) that binds to EGFR. There is not a single fragment of SEQ ID NO: 6 from smallest to largest binds to EGFR in the specification as filed. There is no guidance as to any functional equivalents, nor derivatives, nor are there any working examples of altered sequences that retain binding specificity to EGFR, in turn, effective for treating any disorder related to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung. Let alone preventing any such disorders. Accordingly, enablement is not commensurate in scope with claims that encompass "homologue", "functional portion" or functional portion of any homologue sequence of the full length single chain antibody or anti-EGFR polypeptide.

With respect to pharmaceutical composition, a pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the antibody may be due to an inherently short half-life of the antibody; (2) the antibody may not reach the target area such as the cerebrum, the retina because, i.e. the size of the antibody may not be able to cross the blood brain barrier where the antibody has an effect; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Evidentiary reference Cortez-Retamozo et al (of record, Int J Cancer 98: 456-462, 2002; PTO 1449) teach to be successful as imaging or therapeutic agent for cancer, antibody-based molecules should be small enough to reach the tumor-associated antigen but, in the case of therapeutic antibodies, still large enough to remain for apt periods of time in the circulation. Once the mass of the antibody fragment becomes less than 60 kDa, their administration will require careful management to maintain the blood concentrations required to permit diffusion into the tumor (see page 459, col. 2, Discussion, in particular). Cortez-Retamozo et al teach single-domain monovalent camel antibody exhibited serious short comings because of its rapid pharmacokinetic clearance as it has an in vivo half-life ($T_{1/2}$) of approximately 2 hour in blood

and concluded that nanobody format (being a 15 kDa protein) is not optimal for *in vivo* use in cancer treatment (see page 460, Table 1, page 461, col. 2, in particular). In the absence of *in vivo* working example, it is unpredictable which anti-EGFR polypeptide is efficacious in treating tumor, let alone preventing any disorder related to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung as broadly as claimed.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of in vivo working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 46-54, 61, 63-67, 70-71, 74-75, 78-79, 82, 87, 90-91, and 94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any single domain antibody directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is (1) any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6, (2) a functional portion of SEQ ID NO: 6 wherein the functional portion is capable of binding its target with an affinity of at least 1 x 10^{-6} M; (3) any functional portion of SEQ ID NO: 6 wherein the functional portion comprises any partial deletion of the complete amino acid sequence and still maintains the binding site(s) and protein domain(s) necessary for the binding of and interaction with EGFR as set forth in claim 46, (4) any single domain antibody mentioned above wherein the one or more of the Camelidae amino acids of said single domain antibody are replaced by counterpart amino acids of any human consensus sequence, (5) any single domain antibody directed against any EGFR mentioned above comprising any one or more mutations in the framework region (FR): FR1 positions 1, 5, 28 and 30; the hallmark amino acid at position 44 and 45 in FR2; FR3 residues 74, 75, 76, 83, 84, 93 and 94; and positions 103, 104, 108 and 111 in FR4; wherein the numbering is according to the Kabat numbering as set forth in

claims 46-54, (6) any anti-EGFR polypeptide consisting essentially of two or more single domain antibodies directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is (a) any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6, (b) a functional portion of SEQ ID NO: 6 wherein the functional portion is capable of binding its target with an affinity of at least 1 x 10^{-6} M; (c) any functional portion of SEQ ID NO: 6 wherein the functional portion comprises any partial deletion of the complete amino acid sequence and still maintains the binding site(s) and protein domain(s) necessary for the binding of and interaction with EGFR or (d) any two or more single domains antibodies are identical in sequence fused genetically, or linked to each other directly, or trivalent or tetravalent molecule, (7) any composition comprising any single domain antibody mentioned above as set forth in claims 67, 70-71, 74-75, (8) any pharmaceutical composition comprising any single domain antibody mentioned above and a carrier as set forth in claims 79, 81-82, and (9) any kit comprising any single domain antibody mentioned above as set forth in claim 87, 90-91 and 94.

The specification at page 20 defines "a homologous sequence" as a homologous sequence of the present invention may comprise any additions, any deletions or any substitutions of any one or more amino acids, which do not substantially alter the functional characteristics of the polypeptides of the invention. For the anti-Epidermal Growth Factor Receptor polypeptides, the number of amino acid deletions or substitutions is preferably up to 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 or 70 amino acids". "A homologous sequence according to the present invention may be a sequence modified by the addition, deletion or substitution of amino acids, said modification not substantially altering the functional characteristics compared with the unmodified polypeptide". "A homologous sequence according to the present invention may be a sequence which exists in other *Camelidae* species such as, for example, camel, dromedary, llama, vicuna, alpaca and guanaco".

The specification discloses only isolated single domain antibody VHH from *Camelidae* that binds specifically to Epidermal Growth Factor Receptor (EGFR) such as the ones shown in Table 4 wherein the antibody comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1-22. The specification discloses these single domain antibodies selected for binding to EGFR and for the ability to internalize through cell surface EGFR, see page 50. The specification discloses humanized VHH represented by SEQ ID NO: 13, see page 15, lines 9-21. The specification further discloses the isolated single domain antibody VHH from

Camelidae that binds to EGFR further comprising a single domain antibody VHH that binds to serum albumin corresponds to a sequence selected from the group consisting of SE QI DNO: 27-40 as shown in Table 5. With respect to pharmaceutical composition, there is no in vivo working example whether any such anti-EGFR can treat, much less prevent any disorders relating to any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

At the time of filing, Applicants are not in possession of any single domain antibody that binds to any EGFR directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6 other than the specific single domain antibody that binds to EGFR represented by SEQ ID NO: 6. There is no disclosure as to which amino acids within the sequence represented by SEQ ID NO: 6 to be substituted, deleted and/or added such that the single domain antibody still maintain its binding specificity to EGFR. The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same binding specificity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the SEQ ID NO: 6 and maintains the same biological activity. At the time of the invention, there was a high level of unpredictability associated with altering a protein sequence with an expectation that the protein will maintain the same desired biological activity. For example, it is well established in the art that the even minor changes in the amino acid sequences of the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc Natl Acad Sci USA 1982 Vol 79 page 1979-1983; PTO 892).

Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the length of the antibody heavy chain CDR3 is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and

heavy chains (framework region) is important in maintaining their required conformation for binding and *in vivo* activity.

With respect to claims 49-51, the specification provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to **determine, without undue experimentation**, the positions in the protein are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Vas-Cath, Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence.

The specification does not describe other members of the modified single domain antibody by structure. The specification does not describe the complete structure of any modified single domain antibody having any homology such as 70%, 80% or 90% to SEQ ID NO: 6 or having any mutations in the framework regions (claims 49-51). There is insufficient written description about which amino acids within the full-length sequence of any such anti-EGFR polypeptide or single domain antibody can or cannot be substituted for which amino acids, deleted, added or combination thereof such that it still maintains its conformational tertiary structure and binds specifically to EGFR. Given the innumerous modification to SEQ ID NO: 6, the sequence of single domain antibody has no resemblance to SEQ ID NO: 6, let alone the single domain antibody still binds specifically to EGFR, in turn, effective as a pharmaceutical composition for treating any diseases. Given SEQ ID NO: 6 is the smallest fragment of antibody (single domain antibody) that binds to EGFR, there is not a single fragment of SEQ ID NO: 6 from smallest to largest that binds to EGFR in the specification as filed. As such, any homologous sequence, functional portion of SEQ ID NO: 6 are not adequately described.

Further, the specification defines single domain antibody VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, dromedary, llama, vicuña,

alpaca and guanaco. However, no other single domain antibodies VHH that bind to any EGFR are produced in any species such as dromedary, vicuña, alpaca and guanaco.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of the specific single domain antibodies that bind specifically to EGFR, or serum albumin or EGFR and serum albumin as disclosed in Tables 4-5, the skilled artisan cannot envision the detailed chemical structure of the encompassed anti-EGFR polypeptide, homologous sequence thereof, functional portion thereof or functional portion of any homologous sequence of the full length single chain antibody or anti-EGFR polypeptide for treating any cancer, much less for preventing any disorders susceptible to modulation by the delivery of any EGFR antagonist, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification provides the specific sequence of SEQ ID NO: 6 for the single domain antibody VHH that bind to EGFR for detection assay. The specification does not provide an enabled disclosure of a pharmaceutical composition comprising any single domain antibody that binds to any EGFR directed against any Epidermal Growth Factor Receptor (EGFR), wherein said single domain antibody is any sequence with a homology of more than 70%, 80%, or 90% with SEQ ID NO: 6 or any single domain having any one or more mutations in the framework regions or any anti-EGFR polypeptide consisting essentially of any two or more single domain antibodies such as two or more antibodies are identical in sequences mentioned above for treating and preventing any EGFR associated disorders such as any cancer, rheumatoid

arthritis, psoriasis, or hypersecretion of mucus in the lung using any polypeptide that is functionally equivalent to such without any *in vivo* data.

Therefore, only the specific single domain VHH antibody that bind to EGFR represented by SEQ ID NO: 6 for detection assay, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by US application 2006/0115470 A1 (claimed earliest priority to provisional application 60/425,073 filed Nov 8, 2002; PTO 892).

The US 2006/0115470 A1 application teaches a single domain antibody such as VHH direct against EGFR (see page 3, paragraph [0046], in particular). The reference antibody inherently inhibits or blocks the interaction between EGF and EGFR since the reference antibody is directed against the EGFR. Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,891,996 (issued April 6, 1999; PTO 892) in view of Frenken et al, J Biotechnology 78: 11-21, 2000; PTO 892) and/or Muyldermans et al (J Molecular Recognition 12: 131-140, 1999; PTO 892).

The '996 patent teaches antibody such as humanized antibody directed against EGFR (see entire document, claims of the '996 patent, in particular). The '996 patent teaches antibody that binds to the external domain of the human EGF-R and inhibits the binding of EGF to its receptor at both low and high affinity EGF-R sites which is useful for combating tumor expressing EGFR (see summary of invention, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the antibody is a single domain antibody instead of humanized antibody directed against EGFR.

Frenken et al teach a method of making single domain antibody (VHH) that binds to any antigen from *Camelidae* such as camel, llama or dromedary. The method includes the steps of immunizing the llama with the antigen of interest, obtaining antigen specific heavy chain (VHH) and producing these VHH domain in yeast *Saccharomyces cerevisiae* (see entire document, abstract, page 12, material and methods, page 14, paragraph bridging col. 1 and col. 2, in particular). The advantage in the use of single domain such as VHH domain is that the binding affinity and specificity for the antigen of VHH is similar to Fab fragment derived form a mouse monoclonal antibody, the antigen specific llama VHH fragment is extremely temperature stable, and could easily be secreted by S. cervisiase since the molecular weight and size of the VHH domains is about half that of a scFv fragment (see page 19-20, abstract, in particular).

Muyldermans et al teach that single domain antibody such as VHH has minimal size of antigen-binding fragment and would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph

bridging page 135 and 136, in particular). Natural occurring antibody binding portion such as VHH (single domain) heavy chain antibody isolated from camels, or llamas is the smallest antigen binding fragment (see page 132, col. 2, Figure 1B-C, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make single domain antibody VHH direct against EGFR of the '996 patent using the method of Frenken et al or Muyldermans et al.

One having ordinary skill in the art would have been motivated with the expectation of success to make single domain antibody directed against EGFR because Muyldermans et al teach the smallest size of single domain antibody VHH from camel or llama has the advantages of lower immunogenicity (non-immunogenic), a more rapid clearance from blood for radioisotope imaging of tumor and less non-specific binding would improved penetration in dense tissues that is required for solid tumor (see paragraph bridging page 135 and 136, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to make single domain antibody directed against EGFR because the binding affinity and specificity for the antigen of single domain antibody VHH is similar to Fab fragment obtained form a mouse monoclonal antibody; the single domain antibody from llama VHH is extremely temperature stable, and could easily be secreted by S. cervisiase since the molecular weight and size of the VHH domains is about half that of a scFv fragment as taught by Frenken et al (see page 19-20, abstract, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to make single domain antibody directed against EGFR because the '996 patent teaches antibody that binds to the external domain of the human EGF-R would inhibit the binding of EGF to its receptor at both low and high affinity EGF-R sites and is useful for combating tumor expressing EGFR (see summary of invention, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

14. SEQ ID NO: 6 and 33 are free of prior art.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
October 24, 2008